IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: JOHN DUPRE

Serial No. 09/280,020

Filed: March 29, 1999

For: **TREATMENT OF DIABETES**

Group Art Unit 1644

Examiner P. Nolan

APPEAL BRIEF

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Real Party in Interest

The real party in interest is Amylin Pharmaceuticals, Inc.

Related Appeals and Interferences

A related appeal was filed on January 9, 2001 in case Serial No. 08/737,446, filed January 10, 1997, entitled the same, and before the same examiner.

Status of Claims

Claims 15-34 as appear in Appendix One stand finally rejected and are appealed. All other claims have been cancelled without prejudice to their continued future prosecution.

Status of Amendments

No amendment to the claims has been made subsequent to the final rejection of August 29, 2000. (See Paper 11)

Summary of Invention

For more than a decade, Amylin Pharmaceuticals, Inc., has been a world leader in the research and development of diabetes treatment and prevention. Diabetes is a complex, prevalent, and potentially fatal disease that involves the inability to properly regulate blood glucose levels. The disease is either characterized by the complete inability to produce insulin by virtue of the autoimmune destruction of the cells that produce insulin, pancreatic ß-cells (Type I diabetes or IDDM), or else

by the ability to produce insulin, but only insufficiently or with insufficient effect (Type II diabetes or NIDDM). Insulin reduces blood glucose and is itself regulated, *inter alia*, by the presence of various insulinotropic agents. The different forms of diabetes have historically required very different treatments, which underscores the utility and unobvious nature of the invention.

The invention identifies and exploits glucagon-like peptide 1 (7-36) amide (GLP-1) agonists for the treatment of Type I diabetes. GLP-1 is an insulinotropic agent, i.e., it stimulates the production and release of insulin. Prior to the invention, GLP-1 agonists were thought to be of potential use only in the treatment of Type II diabetes because they work by promoting the release of insulin from functioning B-cells. GLP-1 agonists were not viewed as useful for treating Type I diabetes because people with Type I diabetes lack pancreatic B-cells and, thus, the capability to produce insulin. As such, Type I patients are treated by daily insulin injections, and it was understood that they would not benefit from administration of an insulinotropic agent, such as GLP-1. Surprisingly, Applicant has unequivocally determined that this is not so.

Applicant has unexpectedly discovered that GLP-1 agonists are useful in the treatment of Type I diabetes. For example, based on their ability to delay gastric emptying, the use of

GLP-1 agonists is helpful in the treatment of Type I diabetes working to meter glucose absorption following a meal. Glucose, unchecked, can challenge and overwhelm a diabetic's already compromised system. The use of GLP-1 agonists according to the invention is not only useful for treatment but obviates the Type I diabetic's need to stick to regimented meal schedules to avoid hypoglycemia. With the invention, the Type I diabetic may modulate meal intake and concomitant insulin administration, rendering the Type I diabetic less of a prisoner to this disease. With the invention, the diabetic has a new treatment providing freedom, convenience, and comfort that was not previously available.

To this end, independent claim 20 recites treatment of Type I diabetes in a mammal by orally administering a GLP-1 agonist. Independent claim 15 additionally recites the co-use of insulin in the treatment of diabetes, while dependent claims 16 and 21 specify that the patients are humans, and dependent claims 17 and 22 specify administration in advance of a meal. Dependent claims 18, 19, 23, and 24 all recite the use of specific GLP-1 agonists. Claims 25-34 essentially track the same elements as claims 15-24 except that nasal administration is substituted for oral administration.

Specification support for the various claimed features may be found, e.g., on page 4, lines 20-37 (administration of

glucagon-like peptide 1 (7-36) amide agonists, i.e., glucagon-like peptide 1 (7-37), to mammals, i.e., humans, either alone or in combination with insulin), and page 6, lines 5-30 (delaying gastric emptying through administration prior to a meal), and page 8, lines 9-11 (nasal or oral administration). Examples 1-6, pp. 9-11, are further illustrative and directed to the treatment of Type I diabetics.

Issues

1. Whether Applicant is correct that, within the meaning of 35 U.S.C. § 112, ¶1, the application enables one of ordinary skill in the art to produce the invention of claims 15-18, 20-23, 25-28, and 30-33 without undue experimentation;
2. Whether Applicant is correct that, within the meaning of 35 U.S.C. § 103, claims 15-17, 19-22, 24-27, 29-32, and 34 are unobvious over Gutniak *et al.* in view of U.S. Patent 5,424,286 and D'Allesio *et al.*
3. Whether a double-patenting rejection is appropriate when no patent has as yet issued in the related cases, and when the term of each patent will be measured from the same priority filing date.

Grouping of Claims

Claims 15-34 **do not** stand or fall together. At least four different groupings of claims exist. First, claims 15-19 and 20-24 derive respectively from independent claims 15 and 20. These two sets of claims differ at least with regard to the use of insulin in addition to a glucagon-like peptide 1 (7-36) amide or agonist. Prior to the invention, there was no clear teaching or suggestion in the art to use glucagon-like peptide 1 (7-36) amide or agonist *alone*, let alone *in tandem with* insulin, to treat Type I diabetes mellitus.

Similarly, there is no teaching or suggestion in the art prior to the invention for the timing of administration as recited in claims 17 and 22. As noted in the summary section, above, this timing affords another novel and particularly advantageous alternative to Type I diabetes patients. Thus, this particular administration feature provides another layer of patentability unique to these claims and those claims dependent thereon, namely, 18, 19, 23, and 24.

A further unique feature affording patentability is found in claims 18, 19, 23, and 24 insofar as these do not necessarily require use of an amidated peptide as agonist. This has a pharmaceutical production advantage over an amidated species in that convenient recombinant or synthetic production is afforded

without the need to further chemically modify the end product, e.g., amidate the C-terminus of the peptide.

Similarly, claims 25-34 are directed to nasal rather than oral administration. This means of administration has potentially a more rapid absorption and effect than oral administration, and therefore has added utility in combating diabetic shock in situations where time is of the essence.

In sum, multiple reasons justify separate patentability for the individual claims on appeal.

ARGUMENT I

CLAIMS 15-18, 20-23, AND 25-28 ARE ENABLED WITHIN THE MEANING OF 35 U.S.C. § 112, ¶1 BECAUSE AT THE TIME OF INVENTION ONE OF ORDINARY SKILL IN THE ART COULD SELECT FROM VARIOUS GLP-1 ANALOGS TO BE EMPLOYED WITH THE INVENTION AND BECAUSE THE LAW DOES NOT PERMIT THE PTO TO LIMIT AN INVENTOR TO THE SPECIES DISCLOSED IN A METHOD PATENT.

The Examiner has rejected claims 15-18, 20-23, and 25-28 under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled. In this regard the Examiner focuses on the use of the term, "GLP 1 (7-36) amide agonists." The Examiner has alleged that undue experimentation would be required to ascertain all species of potential agonists.

> [T]he specification, while being enabling for the use of GLP 1 (7-36) amide or GLP 1 (7-37) in treating Type I diabetes nasal or orally, does not <u>reasonably</u> provide

> enablement for the use of any analog to GLP-1 (7-36) amide.
>
> * * *
>
> Since the state of the art teaches that mutations to a known peptide have unknown effects and Applicant has no working examples or guidance in their specification as to what an analogue is or how it would be made, it would be unpredictable and require an undue amount of experimentation to practice the breadth of Applicant's claimed invention.

Paper 11, August 29, 2000, p. 2 (emphasis added). In an effort to support the rejection, the Examiner opines on a selected few of the various factors enumerated in *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988), namely, the presence or absence of working examples, the amount of guidance provided in the specification, the skill level and expectations in the art, and the nature of the invention.

Several reasons underpin the Examiner's error, beginning with the legal tenet that patent applicants are not required to disclose every species that may be encompassed by their claims, even in an unpredictable art. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed Cir. 1988)(citing *In re Angstadt*, 537 F.2d 498, 502-03, 190 USPQ 214, 218 (CCPA 1976)). Further, it is not required that every embodiment in a disclosure be operative in order to be enabling under 35 USC 112, first paragraph. *Atlas Powder Co. v. E.I. Dupont de Nemours & Co.*, 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984); *In re Geerdes*, 491 F.2d 1260, 180 USPQ 789 (CCPA

1974). Nowhere does the Examiner address these bedrock principles. The Examiner has thus failed to carry his burden in attempting to make out a *prima facie* case under § 112.

Notwithstanding the Examiner's failure to make the *prima facie* case, the Examiner also erred in ignoring and/or failing to appreciate timely rebuttal evidence provided by Applicant. Applicant has exemplified over 100 different GLP-1 agonists that were well-known in the art as of the time of filing in addition to those set forth in the specification, citing WO 91/11457, WO 93/18786, WO 90/11296, and EPO application 708179 A3. *See* Response to Office Action, October 18, 1999. Copies of these documents are supplied herewith as attached Exhibits A-D. The following examination of each reveals additional reasons supporting the conclusion that the Examiner's position is wrong.

WO 91/11457, published August 8, 1991 (nearly three full years prior to the filing of the instant priority application) characterized over 100 different GLP-1 (7-36) amide agonists. *See, e.g.*, Figure 2. These analogs consist of amino acid substitutions at positions 7-10 and/or truncation at the C-terminus and/or various other amino acid substitutions in the basic peptide. The Application further describes the substitution of D-amino acid substitutions into the 7 and 8 positions and/or N-alkylated or N-acylated amino acids in the 7 position. Based on WO 91/11457 alone, those in the diabetes art

were aware of numerous GLP-1 (7-36) amide agonists at the time the instant application was filed, albeit for use in the treatment of a wholly different form of diabetes, Type II.

WO 90/11296, published October 4, 1990 (approximately three and a half years prior to the filing of the instant priority application), and entitled "Insulinotropic Hormone" is also directed to GLP-1 agonist analogs and describes numerous analogs expected to have GLP-1 activity. *See, e.g.*, specification, pp. 8-12. Likewise, WO 93/18786, published September 30, 1993 (approximately eight months previous to the priority application's filing), and assigned to Novo Nordisk, cites the previous two applications and confirms that GLP-1 analogs were both plentiful and well known in the art at the time of the invention.

EPO application 708179 A3, assigned to Eli Lilly and Co., and claiming priority to an application filed October 10, 1994, is also consistent with Applicant's position that one of ordinary skill in the art would have known of numerous candidate agonists and how to make them as of the time of filing. For example, this particular application shows that amino acids Lys and Arg are interchangeable at position 19, that Lys 35 may be conjugated to a C_6-C_{10} unbranched acyl group, and that various stabilizing protective groups can be added to the carboxy and amino terminus of the GLP-1 peptide or analogs thereof. *See,*

e.g., specification, pg. 3. Thus, notwithstanding whether the Examiner had made the *prima facie* case, Applicant has more than sufficiently rebutted it.

The Examiner's position is further unsound in view that a patent "need not teach and preferably omits what is well known in the art." *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986), *cert denied*, 480 U.S. 947 (1987); *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991) (what is well-known is preferably omitted); *cf. In re Marzocchi*, 439 F.2d 220, 223-24 (CCPA 1971) (how a teaching is set forth, by specific example or broad terminology, is not important). Although unnecessary in view of the law and facts, Exhibits A-D, all of which predate or are contemporaneous with Applicant's original filing, make plain that numerous GLP-1 agonist compounds were well known and available in the diabetic art.

The patent laws and rules clearly sanction the type of post-filing evidence supplied by Applicant. For example, the Manual of Patent Examining Procedure § 2164.05 provides that documents showing what one skilled in the art knew at the time of filing are appropriately considered during prosecution to confirm enablement. The Federal Circuit is in agreement. *See, e.g., In re Lunkak*, 773 F.2d 1216 (Fed. Cir. 1985) (permitting deposit of biological specimens *post*-filing in satisfaction of the enablement requirement).

In re Wands, cited by the Examiner, also supports Applicant's position. In *In re Wands, the* Federal Circuit enumerated various factors that must be considered when determining whether undue experimentation would be required to practice the claimed invention. Among these were: (i) the breadth of the claims, (ii) the nature of the invention, (iii) the state of the prior art, (iv) the level of skill and knowledge of one of ordinary skill in the art, (v) the level of predictability in the art, (vi) the amount of direction or guidance provided in the specification, (vii) the absence or existence of working examples in the specification, and (viii) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988); MPEP § 2164.01(a). The *Wands* court made clear that no one factor is dispositive and that all factors must be considered. *Id.* at 740. Apparent from these factors, and central to the *Wands* analysis, is that proof may be, and sometimes must be, supplied after filing. Indeed, this is an important purpose behind the submission of Declarations and Affidavits under 37 CFR 1.132.

The Examiner here has failed to considered all of the *Wands* factors, and of those he did consider, he did so incorrectly because he did not consider them in light of all the information

of record, namely, Exhibits A-D. The Examiner originally addressed only the presence or absence of working examples, the nature of the invention, the state of the art, and the predictability of the art. These are but four of the eight *Wands* factors. The Examiner did not discuss the breadth of the claims, the level and knowledge of one of ordinary skill in the art, the amount of direction or guidance provided in the specification, nor the quantity of experimentation needed to make or use the invention. The Examiner thus failed to comply with the *Wands* mandate that all factors be considered. Further, the Examiner was obligated under the law to re-evaluate his analysis of these factors based on Applicant's submission of Exhibits A-D. If he had, he would have reached a very different conclusion.

For example, the Examiner characterized the invention as requiring physiological effect at the receptor level and cited articles discussing how receptor:ligand interactions and modification are generally unpredictable. However, as applied to GLP-1 agonists, this is an inaccurate characterization because, as demonstrated by Exhibits A-D, the GLP-1 agonist art was extremely well-developed as of the time of filing. The Examiner thus miscalculated the true state and level of *this* art. Had the Examiner considered Exhibits A-D, he would clearly have noted that a great amount of knowledge and skill already

existed concerning the production and identification of functional GLP-1 analogs. One of skill would have available many known GLP-1 agonists and not necessarily expend time experimenting with or creating others. Even upon exhaustion of these analogs, however, one of skill would have been well positioned to generate other analogs given the expansive existing platform from which to work.

Evaluation of the remaining *Wands* elements further supports enablement. For example, the invention fundamentally changes treatment of Type I diabetes by providing sufferers thereof with options they did not previously possess. To accomplish this, the invention exploits extensive knowledge concerning GLP-1 agonists, but radically and unobviously extends this knowledge to the treatment of Type I diabetes. *See* Summary of Invention, *supra*. The nature of the invention is thus elegant, yet previously completely unappreciated. The factor, "nature of the invention," thus supports enablement of the claims.

The *Wands* factors, "the amount of direction or guidance provided in the specification" and "the presence or absence of working examples," similarly support enablement, as does the "breadth of the claims." For example, six detailed working examples of the invention are provided in the specification describing treatment of Type I diabetics with GLP-1 analogs. Although these examples detail the use of GLP-1 (7-36) amide as

analog, as demonstrated above, other agonists were known in the art. Thus, substantial and sufficient guidance is provided in the application on how to practice the invention as claimed, and this is supported by the presence of several detailed working examples, as well as knowledge in the art.

From the above, it is thus appreciated that the claims to the invention clearly have support in the specification and knowledge level in the art. When viewed in light of the other seven *Wands* factors, this particular factor likewise supports enablement of the invention, the claims to which are appropriately drawn.

Therefore, based on a proper consideration of the *Wands* factors, and not the incomplete and mistaken considerations urged by the Examiner, the claims are clearly enabled, and the rejection exposed as unsound.

This conclusion takes on added vitality when viewed in light of Judge Rich's opinion in *In re Fuetterer*. 138 USPQ 217 (CCPA 1963). The claims in that case were addressed to a rubber stock for producing tire treads. The claimed rubber stock included "an inorganic salt" that was defined only by being "capable of holding a mixture of [a previously referred to] carbohydrate and [a previously referred to] protein in colloidal suspension in water." Id. at 219.

The PTO Board had affirmed a rejection of the claim as "unduly broad." According to the Board, "Since the alleged novelty appears to reside in the result desired to be obtained by the salts, it is not proper to define the salt by what it is supposed to do rather than what it does." Id. at 221.

Judge Rich promptly disposed of this rejection as unsound:

> The desired result of appellant's invention is limiting the skidding of a tire tread stock on a wet surface. Appellant, in the claims before us, is not claiming this result. A myriad of alternative means for achieving this result can be easily thought of which would not require the particular combination of substances claimed by appellant. Insofar, therefore, as a "functional" claim may mean one which covers all means of arriving at the desired result, although the means by which such result is obtained is entirely different from that disclosed by the applicant, it is apparent that appellant's claims are not "functional."

Id. at 221 (emphasis added). Similarly, the result to be achieved by the use of the invention claimed here is Type 1 diabetes treatment. There are plainly other means for treating Type 1 diabetes (e.g., by the use of insulin) that do not require the particular means claimed by Applicant.

In *In re Fuetterer*, Judge Rich also stressed that patent applicants must be able to obtain claims that adequately protect their inventions, even if experimentation may be required to determine if a product or method falls within the scope of the

claim. Judge Rich described Fuetterer's claim and the PTO rejection as follows:

> The rejection of the claims for "undue breadth" places particular emphasis on (1) an alleged "undue burden upon the public to determine what salts are suitable for obtaining the desired results" (emphasis ours), and (2) an alleged "undue [amount of] experimentation" required of those skilled in the art to determine those salts possessing the "function asserted" by the instant claims. The undue breadth rejection phase of the instant case appears in the following posture. Appellant has described his invention as comprehending the use therein of any inorganic salt capable of performing a specific function in a specific combination and he has disclosed specifically four such salts which are capable of performing this function. The examiner and the board, believing that not all inorganic salts are capable of performing this function and that one skilled in the art would not know offhand which inorganic salts are capable of so functioning, have rejected the claims as "unduly broad."

Id. at 222-223. According to Judge Rich, however, this was all "beside the point" and could not support the PTO's rejection:

> We find the arguments of the board and the examiner relating to experimentation necessary to determine the suitability of undisclosed salts to operate in appellant's claimed combination beside the point. Appellant's invention is the combination claimed and not the discovery that certain inorganic salts have colloid suspending properties. We see nothing in patent law which requires appellant to discover which of all those salts have such properties and which will function properly in his combination. The invention description

> clearly indicates that any inorganic salt which has such properties is usable in his combination.

Id. at 223 (emphasis added). Likewise, Applicant's invention in this case is not the discovery that certain compounds have glucagon-like peptide 1 (7-36) amide agonist activity, but rather that such compounds are useful in the treatment of Type I diabetes.

Judge Rich further emphasized that an applicant's claims may not be restricted so that they are easily avoided simply by identifying an undisclosed compound that will work:

> If others in the future discover what inorganic salts additional to those enumerated do have such properties, it is clear appellant will have no control over them per se, and equally clear his claims should not be so restricted that they can be avoided merely by using some inorganic salt not named by appellant in his disclosure. The only "undue burden" which is apparent to us in the instant case is that which the Patent Office has attempted to place on the appellant.

Id. (emphasis added). Similarly, if others in the future discover other glucagon-like peptide 1 agonists aside from those set out in Applicant's specification with the ability to slow gastric emptying and treat Type I diabetics, Applicant will have no control over them per se (if the claims are limited to the subject matter the Examiner has indicated is enabled). Nevertheless, following *In re Fuetterer*, it is plain that under

the law Applicant's claims cannot be so restricted by the PTO that they can be avoided merely by using some compound not explicitly named in his disclosure.

Accordingly, in view of the arguments and evidence advanced above, Applicant submits that claims 15-18, 20-23, 25-28, and 30-33 are properly enabled, and that the rejection is therefore improper and should be reversed.

ARGUMENT 2

CLAIMS 15-17, 19-22, 24-27, 29-32, AND 34 ARE PATENTABLE UNDER 35 U.S.C. § 103(a) OVER GUTNIAK *ET AL.* IN VIEW OF U.S. PATENT 5,424,286 AND D'ALLESIO *ET AL.* BECAUSE (1) THE EXAMINER HAS FAILED TO CARRY HIS BURDEN IN MAKING THE PRIMA FACIE CASE, (2) BECAUSE THESE DOCUMENTS VIEWED AS A WHOLE ACTUALLY TEACH AWAY FROM THE CLAIMED INVENTION, (3) BECAUSE THESE DOCUMENTS COMBINED DO NOT TEACH OR SUGGEST ONE OR MORE CLAIM LIMITATIONS, AND (4) BECAUSE THE EXAMINER ALLEGES, INCORRECTLY, AN ADMISSION THAT IMPORTS THE SOLUTION INTO THE PROBLEM AND THUS MAKES USE OF HINDSIGHT

a. The Rejection

The Examiner has rejected the foregoing claims as allegedly obvious over Gutniak *et al.* in view of U.S. Patent 5,424,286 and D'Allesio *et al.* The Examiner alleges that GLP-1 analog use to delay gastric emptying was known in the art, that Applicant has admitted such and, further, that in rare situations Type I diabetics still produce insulin which can be potentiated by GLP-1 analogs to render the claims obvious. In reaching this

conclusion, however, the Examiner misunderstands the invention and engages in hindsight.

Prior to Applicant's invention, several of the largest, wealthiest, most shrewd pharmaceutical companies in the world failed to appreciate the value of GLP-1 and GLP-1 agonists to treat Type I diabetes. Three of the leading diabetes companies in the world, Eli Lilly,[1] Novo Nordisk,[2] and Pfizer,[3] each with thousands of sophisticated scientists at their disposal, have all been deeply involved in GLP-1 research. Yet their GLP-1 research programs were devoted to trying to find analogs of GLP-1 for use in the treatment of Type II diabetes, and not Type I diabetes. *See* Exhibits A-D, attached hereto. Each of these diabetes giants, despite years of research, remained completely oblivious to Applicant's important discovery that GLP-1 and GLP-1 agonists can also be used to treat insulin-requiring, i.e., Type I, diabetes.

Notwithstanding this fact, the Examiner continues to allege obviousness over articles that discuss and support meaningful

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[1] *See* http://www.lillydiabetes.com/Products/default.cfm (stating that exogenous insulin is required to treat Type I diabetes); *see also* http://www.lilly.com/about/investor/99report/english/index.html (showing 1999 annual report).

[2] *See* http://www.yourdiabetesworld.com/health/dwk/info/fastfacts/ff_main.asp; http://wwwprod.novonordisk.com/old/investors/annualreports/ar1999/report.asp (showing 1999 annual report).

[3] *See* http://www.pfizer.com/hml/know/knowglucotrolxl.html#3 (stating that Type I diabetics cannot produce insulin while Type II diabetics can);

GLP-1 use only in Type II diabetics, and that provide no or only control data for Type I patients. The Examiner extrapolates, incorrectly, that the data and discussion in these articles supports treatment of Type I diabetics. As demonstrated below, a complete examination of these articles reveals that only Type II treatment is envisioned from these articles, not Type I treatment, and that one of skill in the art at the time of filing would have been skeptical of any other use. None of the articles, alone or in any combination, teach or suggest the claimed invention.

b. The legal standard for obviousness

Legal obviousness requires that an alleged combination of art references reflect the specific combination claimed. *In re Dance*, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998). Further, it is well understood that before the PTO may combine the disclosures of alleged references, there must be some suggestion for doing so, found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Jones*, 21 USPQ2d 1941 (Fed. Cir. 1992) (citing *In re Fine*, 5 USPQ2d 1596, 1598-99 (Fed. Cir. 1988)). There must be some objective suggestion in the art to do what the applicant has claimed. *See, e.g., Ex parte*

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see also http://pfizer.com/pfizerinc/investing/investingfrm.html (for annual reports)

Obukowicz, 27 USPQ2d 1063, 1065 (Bd. Patent App & Inf. 1992), which confirms that:

> In proceedings before the Patent and Trademark Office, the examiner bears the burden of establishing a prima facie case of obviousness based upon the prior art. *In re Piasecki*, 745 F.2d 1468, 1471-72, 223 USPQ 785, 787-88 (Fed. Cir. 1984). The examiner can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references. *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ 2d 1596, 1598 (Fed. Cir. 1988). Indeed, the teachings of the references can be combined only if there is some suggestion or incentive to do so. *ACS Hospital Systems Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984).

Further, the teaching or suggestion to combine must be "clear and particular," and not merely "[b]road conclusory statements regarding the teaching of multiple references." *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999). Also, an alleged reference "must be read not in isolation, but for what it fairly teaches in combination with the prior art as a whole."

Additionally, in making the obviousness determination, one must not import the solution into the problem. To do so admits of impermissible hindsight. *Monarch Knitting Machinery Corp. v. Fukuhara Industrial & Trading Co., Ltd.*, 139 F.3d 1009, 45 USQP2d 1977 (Fed. Cir. 1998). Put differently,

> to imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art

> reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher.

In re Fine, 837 F.2d at 1074, 5 USPQ2d at 1598 (Fed. Cir. 1988), citing *W.L. Gore Assoc. v. Garlock*, 721 F.2d 1540, 1553 220 USPQ 303, 312-13 (Fed. Cir. 1983).

As demonstrated below, the Examiner fails to establish every element of the claims in his rejection, and further fails to establish a clear and proper motivation to combine the elements alleged to be present.

c. Analysis

The broadest claims on appeal, 20 and 30, respectively recite methods of treating Type I diabetes by nasal and oral administration of GLP-1 agonists to delay gastric emptying:

> A method of <u>treating Type I diabetes</u> mellitus in a mammal comprising administering an effective amount of a glucagon-like peptide 1 (7-36) amide agonist, wherein said glucagon-like peptide 1 (7-36) amide agonist <u>delays gastric emptying</u> and wherein said glucagon-like peptide 1 (7-36) amide agonist is administered [<u>nasally or orally</u>].

(Emphasis added). All of the appealed claims have these terms in common. As demonstrated below, the underscored terms are plainly <u>not</u> found in any combination of the alleged references. Hence the Examiner has not made a *prima facie* case of

obviousness. Additionally, the Examiner has failed to properly consider Applicant's real world evidence of non-obviousness.

(i) Gutniak *et al.*

Gutniak *et al.*, *N. Eng. J. Med.* 326:1316-1322 (1992), allegedly reports laboratory experiments involving intravenous infusion of GLP-1 (7-36) amide into diabetic patients, including (1) Biostator experiments in which patients were connected to a closed-loop insulin-infusion system and received insulin intravenously to keep their blood glucose concentrations normal;[4] and (2) hyperinsulinemic-normoglycemic-clamp experiments, in which blood glucose concentration was kept constant and glucose utilization calculated.[5]

Although Gutniak *et al.* monitored both Type I and Type II diabetic patients, Gutniak *et al.* concluded only that Type II diabetes is potentially treatable using GLP-1 agonists, and it

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[4] In the Biostator experiments, if blood glucose was above a certain level, the Biostator increased the rate of insulin infusion to maintain a constant blood glucose level. This was performed on several Type I and Type II diabetics. In the Type I diabetics, the infusion of GLP-1 (7-36) amide reportedly decreased the post-prandial increase in the blood glucose and plasma-free insulin concentrations. *See, e.g.*, pp 1318, col 2. This infusion was said to lower the meal-related requirements for exogenous insulin and also to lower the calculated isoglycemic meal-related insulin requirement. *Id.*, pp. 1319, col. 1.

[5] In the hyperinsulinemic-normoglycemic clamp studies, insulin was infused at a relatively high rate (0.8 mU/kg/min), and glucose was maintained at a concentration of 4.7 nmol/L by varying the rate of infusion. Thus, if the blood glucose concentration fell below a certain level, the rate of glucose infusion was increased. In several subjects with Type I diabetes, the infusion of GLP-1 (7-36) amide was reported to increase glucose utilization, as compared with the infusion of saline (*see* pp. 1319, col. 1) and this was said to indicate increased insulin sensitivity.

contains no teaching or suggestion for treatment of Type I diabetes:

> Conclusions. GLIP has an antidiabetogenic effect, and it may therefore be useful in the treatment of patients with NIDDM [Type II diabetes].

Pp. 1316, Abstract (emphasis added). Inherent in this conclusion is a lack of any appreciation for the ability of GLP-1 to treat Type I diabetes. For example, in Type I diabetes insulin is, for all intensive purposes, completely lacking. It would therefore have been unexpected that an agent which was believed useful only for its ability to *stimulate* insulin production could also be useful in the treatment of patients *incapable* of producing insulin. Type I patients would not exhibit an appreciable secretory response to GLP-1. Administration to such patients, prior to the invention, would therefore be expected to be futile.

That Gutniak identifies the further ability of GLP-1 to increase sensitivity to, and hence lower the requirement for, insulin, does not support the Examiner's conclusion. Increased insulin sensitivity does not eliminate the need for exogenous insulin in Type I patients. Also, insulin resistance typifies Type II diabetes, not Type I diabetes. Hence, increased insulin sensitivity would have been viewed as useful only in the treatment of Type II diabetes. Altering normal insulin

sensitivity in Type I patients would have been counterintuitive to the overall objective of returning the Type I diabetic patient's system to normalcy. Moreover, increasing insulin sensitivity in such individuals would only magnify the potential for dangerous hypoglycemia in the presence of exogenously administered insulin.

Gutniak's conclusion that GLP-1 represents a potential treatment for only Type II diabetes underscores this point:

> Our study demonstrates that at least in the short term, the administration of GLIP decreases postprandial insulin requirements and plasma insulin concentration in [Type II] patients... Therefore, the peptide may have a role in the treatment of some patients with diabetes.

Gutniak *et al.*, page 1321 (emphasis added). Gutniak did not expect that *all* diabetes forms, especially Type I diabetes, would be amenable to treatment with GLP-1. By contrast, and without a proper foundation, the Examiner insists that Gutniak suggests treatment of all diabetic patients. The Examiner can only conclude this using hindsight, and by keying on select portions of Gutniak while ignoring the document and art as a whole.[6] Gutniak absolutely does not, as the Examiner maintains, teach treatment of Type I diabetes with GLP-1.

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[6] *See, e.g., In re Wesslau*, 147 USPQ 391, 393 (CCPA 1965) ("It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.")

Nor does Gutniak teach the claim limitations of nasal or oral administration and delayed gastric emptying. Gutniak is therefore deficient in claim elements and motive for treatment of Type I diabetes using GLP-1 agonists. Significantly, and as demonstrated below, neither the '286 patent nor the D'Allesio article supply what Gutniak *et al*. lacks.

(ii) The '286 patent

The '286 patent relates to exendin polypeptides and pharmaceutical compositions comprising exendin polypeptides, not GLP-1. The lone mention of GLP-1 at column 1, lines 49-68 is provided merely as an introduction to the exendin invention. Although the patent cites Gutniak *et al*., it actually *defers* to Gutniak's findings, and provides no additional data. It is therefore highly significant that the '286 patent mischaracterizes Gutniak as suggesting the possible treatment of all forms of diabetes, when in fact a reading of Gutniak by one of ordinary skill in the art at the time would only have suggested Type II diabetes treatment. This is understandable given that the subject of the '286 patent is also treatment of Type II (and not Type I) diabetes.

The Examiner therefore seizes on, a best, a misstatement in the '286 patent that, as explained above, has absolutely no foundation in the source in which it allegedly originates, Gutniak. Indeed, the mistake would have readily evoked

skepticism in the person of ordinary skill at the time of invention without resort to the instant specification. Further, and as demonstrated *infra*, the discussion of Gutniak in the '286 patent must, by law, be read in light of the entire Gutniak *et al.* article and the entire '286 patent, and not select portions thereof.

Even assuming that the '286 patent does not misspeak or overspeak with respect to Gutniak (which it plainly does), the '286 patent still does not teach treatment employing delayed gastric emptying and nasal or oral GLP-1 agonist administration. The addition of the '286 teachings to Gutniak therefore adds nothing, and claim element correspondence is still lacking.

(iii) D'Alessio *et al.*

D'Alessio *et al.*, *J. Clin. Invest.* 93:2263-66 (1994) , does not remedy the deficiencies of Gutniak. D'Alessio only focuses on the influence of GLP-1 on intravenous glucose tolerance ("glucose effectiveness") in healthy nondiabetic adults. D'Alessio absolutely fails to identify, teach, or suggest the use of nasal or orally administered GLP-1 agonists for the treatment of Type I diabetes through delayed gastric emptying. This is clear from the following statement in D'Alessio:

> We cannot determine the site where GLP-1 exerts its action to enhance glucose effectiveness, since the indices derived by the minimal model represent whole body glucose kinetics.

Pp. 2265, col. 2, ¶ 5, third sentence. This illustrates D'Alessio's focus on systemic glucose disposition once the glucose has already entered the system, rather than its initial entry into the system via the abdominal cavity following ingestion of a meal. Thus, D'Alessio clearly teaches away from delayed gastric emptying and the claimed invention.

Furthermore, and consistent with Gutniak, D'Allesio is laced with discussion of implications for Type II diabetes treatment, but contains virtually no discussion addressed to the possibility for use in the treatment of Type I diabetes.

In addition to the fact that Gutniak, D'Alessio, and the '286 patent cannot be combined to teach Type I diabetes treatment with GLP-1 agonists, these articles combined still do not teach treatment moderated by delayed gastric emptying, and mediated by nasal or oral GLP-1 agonist administration. The combined teachings of D'Alessio and the '286 patent therefore add nothing to Gutniak.

(iv) The alleged admission

None of Gutniak, the '286 patent, nor D'Allesio teach a "delay in gastric emptying," as claimed. Instead, the Examiner conclusorily alleges that a particular statement in Applicant's specification constitutes an "admission." *See* Office Action, December 9, 1999, Paper 17, pg. 3. The alleged "admission"

reads: "GLIP is known to cause delay of gastric emptying in humans and other mammals (Wettergren *et al.*, (1993), Digestive Diseases and Sciences, v. 38, p. 665)." Specification, pg. 5, lines 34-36. There are multiple problems with the Examiner's position.

First, the alleged admission does not appear in the "Background of the Invention" section of the application. Instead, it appears in the "Detailed Description of the Invention" section. (emphasis added). Second, the statement does not in any way state or suggest a knowledge within the prior or background arts going to diabetes treatments. Of all the cases examined by Applicant in which admissions were found to have been made in the specification, those admissions either occurred in the background art section, or else were coupled with an affirmative statement of their status as "prior art." *See, e.g., Ex parte Nagano*, 219 U.S.P.Q. 1130 (Bd. Pat. App. & Int. 1983)(specification described invention as "improvement" over the prior art); *In re Nomiya*, 509 F.2d 566 (CCPA 1975)(figure legend explicitly captioned, "Prior Art"); *accord In re Hellsund*, 474 F.2d 1307 (C.C.P.A. 1973); *see also In re Garfinkel*, 437 F.2d 1000, 1004 (C.C.P.A. 1971)(attempt to swear behind reference taken as admission of that reference's prior art status); *In re LoPresti*, 333 F.2d 932 (C.C.P.A. 1964)(applicants indicated that invention constituted

"improvement" over cited prior art reference). Thus, a mere statement that "something is known," without more, does not establish an admission.

Further, the journal title for the alleged Wettergren reference is "Digestive Diseases and Sciences." On its face, this title actually teaches away from the invention insofar as it equates slowed gastric emptying with a digestive disease. Clearly, an important part of the claimed invention is the exact opposite—the unobvious harnessing of delayed gastric emptying in disease *treatment*. This emphatically demonstrates the failure by the Examiner to consider the "whole" of the record and to "clearly and particularly" point out how the alleged references and alleged admissions render the claimed invention obvious. *In re Merck & Co., supra; In re Dembiczak, supra.*

One is therefore led to the inescapable conclusion that the Examiner, by borrowing from the "Detailed Description of the Invention" section of the specification, "imports the solution into the problem" and therefore uses hindsight in formulating his rejection. This also underscores that the Examiner has failed to carry his burden in making the *prima facie* case. *See Monarch Knitting, supra; Heidelberger Druckmaschinen AG v. Hantscho Commercial Products, Inc., 21 F.3d 1068 (Fed. Cir. 1993)* ("The motivation to combine the references cannot come from the invention itself").

(v) The alleged references, considered as a whole, teach away from the claimed invention

Notwithstanding the impropriety of the alleged admission, one of ordinary skill in the art at the time the invention was made would not have been motivated to treat Type I diabetes with GLP-1 agonists because Gutniak *et al.* actually teaches or suggests, at most, only Type II diabetes treatment. Moreover, D'Allesio, which cites Gutniak, similarly teaches away in its focus on the ability of GLP-1 to act as an insulinotropic agent which, as explained above, cannot remedy Type I diabetes. Therefore, in maintaining the rejection the Examiner contravenes law which provides that evidence of "teaching away" must be considered, and that such can completely undermine the necessary motivation to combine.

In *Gambro Lundia AB v. Baxter Healthcare Corp.* 42 USPQ2d 1378, 1383 (Fed. Cir. 1997), for example, the Federal Circuit reversed a district court that held various claims of a patent invalid for obviousness over evidence that taught away from the invention. In the present case, the line of development flowing from the disclosure of the alleged reference does not lead to the result sought by Applicant and is actually antithetical to the claims without the help of the specification. Similarly, in *Monarch Knitting Machinery Corp. v. Sulzer Moat GmbH*, 45 USPQ2d 1977 (Fed. Cir. 1998), the Court upheld a denial of summary

judgment where strong evidence of teaching away existed in the art.

Related to the Examiner's failure to acknowledge evidence that teaches away from the claimed invention, the Examiner also violates other legal tenets. For example, the Examiner appears to be relying only on select portions of Gutniak *et al.* and other cited documents in making his rejection, while ignoring other portions which do not support his position. *See, e.g., In re Wesslau*, 147 USPQ 391,393 (CCPA 1965) ("It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.") As discussed further below, the Examiner has also failed to clearly and particularly show how the claimed feature of nasal or oral administration is made obvious by the alleged references. This complements the absence of any teaching or suggestion of "delayed gastic emptying," and demonstrates that multiple claim elements are still missing from the combined art cited by the Examiner. *See, e.g., In re Dance, supra* ("specific" combination not shown); *In re Dembiczak, supra* (Examiner's rejection must clearly and particulary show the proper combination and the motivation to combine to achieve that combination).

ARGUMENT 3

THE PROVISIONAL REJECTION OF CLAIMS 15-34 FOR ALLEGED NON-STATUTORY DOUBLE PATENTING IS INAPPROPRIATE BECAUSE THE LAW HAS CHANGED WITH RESPECT TO CALCULATION OF PATENT TERM, MAKING THE TERM OF EACH PATENT ISSUED ON THE SUBJECT APPLICATIONS THE SAME, AND ELIMINATING ANY POSSIBILITY OF AN IMPROPER EXTENSION OF THE "RIGHT TO EXCLUDE."

The Examiner has maintained a double-patenting rejection over US Ser. No. 08/737,446 in view of WO 93/18786, insisting that a terminal disclaimer be filed, and stating:

> The non-statutory double patenting rejection, whether of the obviousness-type of non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. .

The Examiner's rejection is inappropriate in light of law changes implemented in 1995[7] that mandate an identical base patent term for each patent issuing on the subject applications. Thus, no policy is offended and no improper extension of rights would occur. A terminal disclaimer would therefore serve no purpose.

Accordingly, Applicant respectfully submits that this ground of rejection is inappropriate and should be withdrawn.

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[7] Congress amended 35 U.S.C. 154 by changing the patent term for patents issued on applications filed after June 7, 1995 to

CONCLUSION

For all of the foregoing reasons, Applicant submits that all outstanding rejections of claims and objections to the specification should be reversed and seeks an early ruling to that effect.

Dated: 2/27/01

Respectfully submitted,

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twenty years from original (priority) filing. Previously, the term had been 17 years from issuance.

Appendix One

15. A method of treating Type I diabetes mellitus in a mammal comprising administering to said mammal an effective amount of an insulin and an effective amount of a glucagon-like peptide 1 (7-36) amide agonist, wherein said glucagon-like peptide 1 (7-36) amide agonist delays gastric emptying and wherein said glucagon-like peptide 1 (7-36) amide agonist is administered orally.

16. A method according to claim 15 wherein said mammal is a human.

17. A method according to claim 16 wherein said insulin and said glucagon-like peptide 1 (7-36) amide agonist are administered to the human at a selected time prior to ingestion of a meal.

18. A method according to any of claims 15-17 wherein said glucagon-like peptide 1 (7-36) amide agonist is glucagon-like peptide 1 (7-37) [(7-36)].

19. A method according to any of claims 15-17 wherein said glucagon-like peptide 1 (7-36) amide agonist is glucagon-like peptide 1 (7-36) amide.

20. A method of treating Type I diabetes mellitus in a mammal comprising administering an effective amount of a glucagon-like peptide 1 (7-36) amide agonist, wherein said glucagon-like peptide 1 (7-36) amide agonist delays gastric emptying and wherein said glucagon-like peptide 1 (7-36) amide agonist is administered orally.

21. A method according to claim 20 wherein said mammal is a human.

22. A method according to claim 21 wherein said glucagon-like peptide 1 (7-36) amide agonist is administered to the human at a selected time prior to ingestion of a meal.

23. A method according to any of claims 20-22 wherein said glucagon-like peptide 1 (7-36) amide agonist is glucagon-like peptide 1 (7-37) [(7-36)].

24. A method according to any of claims 20-22 wherein said glucagon-like peptide 1 (7-36) amide agonist is glucagon-like peptide 1 (7-36) amide.

25. A method of treating Type I diabetes mellitus in a mammal comprising administering to said mammal an effective amount of an insulin and an effective amount of a glucagon-like peptide 1 (7-36) amide agonist, wherein said glucagon-like peptide 1 (7-36) amide agonist delays gastric emptying and wherein said glucagon-like peptide 1 (7-36) amide agonist is administered nasally.

26. A method according to claim 25 wherein said mammal is a human.

27. A method according to claim 26 wherein said insulin and said glucagon-like peptide 1 (7-36) amide agonist are administered to the human at a selected time prior to ingestion of a meal.

28. A method according to any of claims 25-27 wherein said glucagon-like peptide 1 (7-36) amide agonist is glucagon-like peptide 1 (7-37) [(7-36)].

29. A method according to any of claims 25-27 wherein said glucagon-like peptide 1 (7-36) amide agonist is glucagon-like peptide 1 (7-36) amide.

30. A method of treating Type I diabetes mellitus in a mammal comprising administering an effective amount of a glucagon-like peptide 1 (7-36) amide agonist, wherein said glucagon-like peptide 1 (7-36) amide agonist delays gastric emptying and wherein said glucagon-like peptide 1 (7-36) amide agonist is administered nasally.

31. A method according to claim 30 wherein said mammal is a human.

32. A method according to claim 31 wherein said glucagon-like peptide 1 (7-36) amide agonist is administered to the human at a selected time prior to ingestion of a meal.

33. A method according to any of claims 30-32 wherein said glucagon-like peptide 1 (7-36) amide agonist is glucagon-like peptide 1 (7-37) [(7-36)].

34. A method according to any of claims 30-32 wherein said glucagon-like peptide 1 (7-36) amide agonist is glucagon-like peptide 1 (7-36) amide.